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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/465,444	12/16/99	FOUNDS H	361331-0004

HM22/0531

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EXAMINER	
NOLAN, P	
ART UNIT	**PAPER NUMBER**
1644	2

DATE MAILED: 05/31/00

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/465,444	Fornels et al.
Examiner	**Group Art Unit**
Nolan	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp siti n of Claims

☒ Claim(s) 1-16 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 1-8 is/are allowed.

☒ Claim(s) 9-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachm nt(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. This application is a Reissue application of U.S. Patent 5,698,197.

2. Claims 1-16 are pending.

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.
See form PTO 948.

4. Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which inhibited to bind its antigen by glycated lysine or 6-aminocaproic acid at a IC50 of 5 X 10^{-4} M, does not reasonably provide enablement for an IC50 of less than 5 X 10^{-4} M. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to use the invention commensurate in scope with these claims.

Applicant has no working examples in their specification demonstrating an antibody which is inhibited by glycated lysine or 6-aminocaproic acid at a IC50 of less 5 X 10^{-4} M, there is no guidance in the specification teaching one of skill in the art how to arrive at an antibody with said functional limitations. Since monoclonal antibody binding specificity is art recognized to be highly variable, it would be unpredictable and require an undue amount of experimentation for one of skill in the art to practice the full breadth of Applicant's claimed invention.

5. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 misspelled chimeric, correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior

art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 9-11 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Makita et al. (J. Biol. Chem., 1992) or Makita et al. (Science, 1992) both in view Harlow et al. (Antibodies, 1988).

Makita et al. (J. Biol. Chem., 1992) teach preparation of polyclonal antibodies to an AGE epitope which forms *in vitro* after incubation of glucose with ribonuclease (RNase). This antiserum proved suitable for the detection of AGEs which form *in vivo*. Both diabetic tissue and serum known to contain elevated levels of AGEs readily competed for antibody binding. Cross reactivity studies revealed the presence of a common AGE epitope which forms after the incubation of diverse proteins with glucose. These data suggest that tissue AGEs which form *in vivo* appear to contain a common immunological epitope which cross-reacts with AGEs prepared *in vitro*, supporting the concept that immunologically similar AGE structures from the incubation of sugars with different proteins (see Abstract, in particular). Makita et al. also teach an immunochemical assay for proteins modified by advanced glycosylation using antibodies specific for a common AGE epitope *in vivo* (page 5133, in particular). Further, Makita et al. teach that AGE modification was observed to compete for antibody binding when it is present on diverse carrier proteins. Thus, glucose-derived AGE-RNase, Glc-6-P-derived AGE-HSA, glucose-derived AGE-LDL, and glucose derived AGE-collagen IV all demonstrated specific inhibition of antibody binding to glucose-derived AGE-BSA (page 5135, in particular).

Makita et al. (Science, 1992) teach using antibodies against AGEs developed for the detection of *in vivo* formed AGEs in a competitive ELISA to measure hemoglobin-linked AGEs in red cell hemolysates (page 651, in particular).

The claimed invention differs from the prior art teachings by specifying a monoclonal antibody with particular binding IC50's to glycated lysine or 6-aminocaproic acid and further a monoclonal antibody that is a murine IgG isotype, a monoclonal antibody which is labeled, antibody fragments, and anti-AGE with a pharmaceutically acceptable carrier. However, Harlow et al. teach production of monoclonal antibodies (see page 148, in particular). Harlow et al. also teach that polyclonal sera contain mixed populations of antibodies with a variety of specificity and affinity for antigen which creates problems in immunochemical techniques and that hybridoma cell lines produce unlimited quantities of monoclonal antibodies with homogeneous specificity

and affinity for antigen (page 141, in particular). Further, Harlow et al. teach selecting class switch variants. These shift variants generally are useful in switching from IgM to IgG. The different classes or subclasses of antibodies have properties that make them more or less useful in various immunochemical techniques. These differences make the preparation of antibodies of certain classes or subclasses very valuable (page 238, in particular). Harlow et al. also teach labeling antibodies and that a wide range of immunological techniques depend on the use of labeled antibodies (page 321, in particular). Further, Harlow et al. teach generation of proteolytic fragments of antibodies such as Fab, Fc, and $F(ab)_2$. Harlow et al. also teach that the use of an intact antibody molecule in some immunochemical techniques introduces certain problems and that these problems and can be overcome by using fragments of the antibodies (page 626, in particular). Lastly, Harlow et al. teach that purified antibodies are stored in phosphate buffered saline (PBS), which is well known in the art as a pharmaceutically acceptable carrier (see page 287, in particular).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to generate hybridomas and monoclonal antibodies given the teachings of Makita et al., Makita et al. and Harlow et al. because Harlow et al. teach that hybridomas produce monoclonal antibodies that have homogeneous specificity and affinity for antigen thereby providing an expectation of success that monoclonal anti-AGE antibodies will have and IC50 for glycated lysine or 6-aminocaproic acid at 5×10^{-4} M, since monoclonal antibodies that bind with high specificity are art recognized to be desirable since less antibody is required to perform an assay.

Further it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to switch monoclonal antibodies from IgM to IgG isotypes as taught by Harlow et al. because the different classes or subclasses of antibodies have properties that make them more or less useful in various immunochemical techniques, thereby providing an expectation of success that a IgG monoclonal antibody to *in vivo* AGE proteins can be used in various immunochemical techniques.

Further it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to label the anti-AGE monoclonal antibody taught by Makita et al, Makita et al. and Harlow et al. because a wide range of immunological techniques depend on the use of labeled antibodies thereby providing an expectation of success that labeled anti-AGE monoclonal antibodies can be used in immunoassays.

Further it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to generation of proteolytic fragments of antibodies such as Fab, Fc, and $F(ab)_2$ of anti-AGE monoclonal antibodies as taught by Makita et al, Makita et al. and Harlow et al. because use of an intact antibody molecule in some immunochemical techniques introduces certain problems and that these problems and can be overcome by using fragments of the antibodies thereby providing an expectation of success that proteolytic fragments of anti-AGE monoclonal antibodies can be used in immunoassays.

Further it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to store the monoclonal antibodies generated in PBS as taught by Makita et al, Makita et al. and Harlow et al. because purified antibodies are routinely stored in PBS.

7. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Makita et al. (J. Biol. Chem, 1992), Makita et al. (Science, 1992) and Harlow et al. (Antibodies, 1988) as applied to claims 1, 2, 4, 5, 7, and 8 above, and further in view of Queen et al. (Proc. Natl. Acad. Sci. USA, 1989).

Makita et al. (J. Biol. Chem, 1992), Makita et al. (Science, 1992) and Harlow et al. (Antibodies, 1988) have been discussed supra.

The claimed invention differs from prior art teachings only by specifying a humanized or chimeric human-murine antibody. However, Queen et al. teach generation of human-mouse chimeric antibodies. Further, Queen et al. teach that the immune response against a murine monoclonal antibody may be potentially reduced by transforming it into a chimeric antibody (page 10029, in particular).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to generate humanized antibodies using the teachings of Queen et al. with the anti-AGE monoclonal antibody taught by Makita et al. (J. Biol. Chem, 1992), Makita et al. (Science, 1992) and Harlow et al. (Antibodies, 1988) because humanized antibodies reduced the immune response against a murine monoclonal antibody.

8. Applicant is notfied that claims 1-8 in their present form are free of the prior art.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick Nolan whose telephone number is (703) 305-1987. The examiner can normally be reached on Monday through Friday from 8:30 am to 4:30 pm.

10. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for our group, 1644, is (703) 305-7939. Any inquiry of a general nature relating to the status of this application or proceeding should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Patrick J. Nolan

Patrick J. Nolan, Ph.D.
Patent Examiner, Group 1640
May 25, 2000